CASE REPORT

Sinonasal Undifferentiated Carcinoma: Current Trends in Treatment

Karen T. Pitman, LCDR MC USN,
Peter D. Costantino, M.D.,*
and Lorenz F. Lassen, CDR MC USN

Abstract—Sinonasal undifferentiated carcinoma (SNUC) is a rare and highly aggressive neoplasm of the paranasal sinuses, which has recently been characterized as a distinct pathologic entity. The prognosis for patients with SNUC is poor. Early case reports describe patients with lesions that were clinically advanced at initial presentation and surgically unresectable. Survival was reported in months after treatment with chemotherapy and radiation. As more experience was gained with treatment of SNUC, it was found that aggressive, combined surgical therapy of lesions previously considered unresectable has shown increased survival. We report a case of a 38-year-old man with SNUC originating in the posterior ethmoid, extending into the anterior cranial fossa and orbit, who was treated with preoperative hyperfractionated radiation therapy, chemotherapy, and craniofacial resection. (*Skull Base Surgery, 5(4):269–272, 1995*)

Sinonasal undifferentiated carcinoma (SNUC) is a rare and highly aggressive malignancy of the paranasal sinuses that was first identified as a separate entity in the 1980s. Before that time, highly malignant, rapidly growing neoplasms that had been identified as anaplastic or undifferentiated carcinoma were in all probability SNUC. SNUC must be distinguished from other small to medium-sized cell sinonasal neoplasms because of its aggressive behavior and often fulminant clinical course.[1,2]

Typically, patients with SNUC present with an advanced stage neoplasm following rapid onset of symptoms and early proptosis. Improved diagnostic radiographic imaging now offers excellent staging information for paranasal sinus malignancies. Immunohistochemistry (IHC) has dramatically improved our ability to differentiate various small to medium-sized cell malignancies of the paranasal sinuses. The recent increase in the number of published reports of SNUC is probably a result of improvements in our diagnostic capability rather than a "new tumor."[3]

The optimal treatment for SNUC has yet to be determined. We present a case with our management, follow-up, and future recommendations.

CASE PRESENTATION

A 38-year-old man was referred to our clinic for evaluation of headaches, diplopia, and decreased ability to smell. The past medical, social, and surgical history were unremarkable. There was no nasal dyspnea or epistaxis.

Physical examination showed a mass on the lateral wall of the right nasal cavity that medially displaced the right middle turbinate. Ophthalmologic examination showed right eye papilledema and 3 ml of right eye proptosis. Diplopia was present on upward and lateral gaze and there was decreased right eye adduction. The remainder of the physical examination was normal and metastatic workup was negative.

Magnetic resonance imaging (MRI) of the head and sinuses showed an expansile lesion centered at the right

Skull Base Surgery, Volume 5, Number 4, July 1995 Department of Otolaryngology-Head and Neck Surgery, Naval Medical Center, Portsmouth, Virginia *Present address: Department of Otolaryngology-Head and Neck Surgery, Loyola University Chicago, 2160 South First Street, Maywood, IL 60153 The opinions or assertions expressed herein are those of the authors and are not construed as official or as reflecting the views of the Department of the Navy or Department of Defense Reprint requests: Dr. Pitman, Department of Otolaryngology-Head and Neck Surgery, Naval Medical Center, Portsmouth, VA 23709-5100

posterior ethmoid and sphenoid (Fig. 1). The mass extended into the anterior cranial fossa, right orbit and posteriorly to the orbital apices and cavernous sinus. The mass irregularly enhanced with gadolinium contrast medium. Computed tomography (CT) confirmed bony erosion of the lamina papyracea and planum sphenoidale.

The patient was taken to the operating room for an endoscopic intranasal biopsy of this lesion. Pathologic analysis confirmed SNUC.

Treatment

The patient underwent neoadjuvant radiation therapy consisting of twice daily treatments of 160 cGy via anteroposterior, right and left lateral fields for a total dose of 64 Gy to the tumor mass. Intranasal examination of the tumor mass showed marked regression at the completion of radiation therapy. He then received four cycles of etoposide and cisplatin. Dosage regimens were etoposide 100 mg/m^2 and cisplatin 30 mg/m^2 intravenously on days 1, 2, and 3 of each month for 4 months. Follow-up MRI 6 months after initial diagnosis showed shrinkage of the lesion and cystic changes consistent with tumor necrosis (Fig. 2). Seven months after initial diagnosis, the patient underwent an uncomplicated anterior craniofacial resection for extirpation of the tumor. The dura in direct contact with the cribriform plate was resected, and intraoperative frozen section pathologic analysis of the adjacent dura and periorbita was negative for tumor. The defect was closed with a dural graft and pericranial flap. The patient did well postoperatively and was discharged on postoperative day 8.

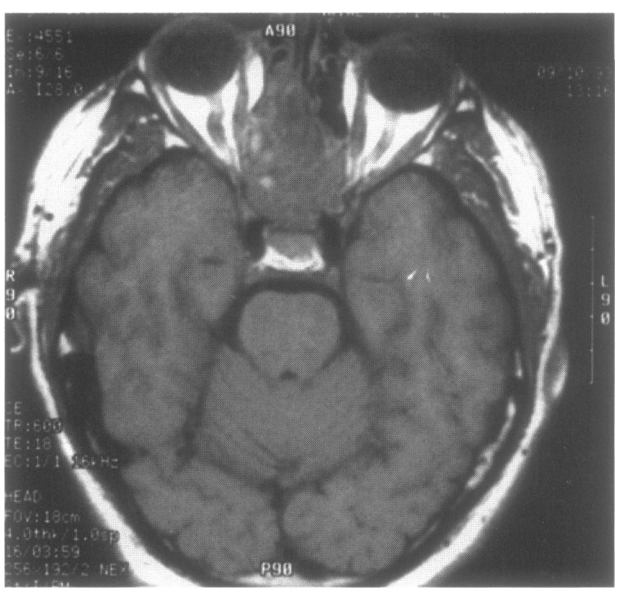

Figure 1. T_1-weighted magnetic resonance image before treatment.

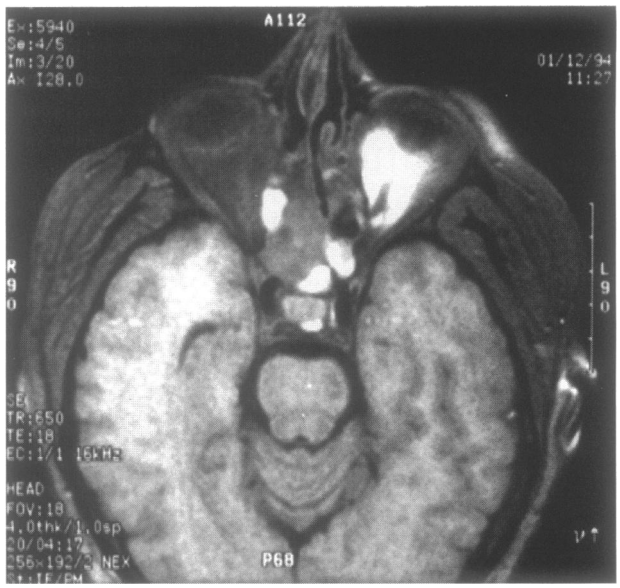

Figure 2. T_1-weighted magnetic resonance image after neoadjuvant therapy.

Follow-up

Our patient returned to work 3 months after surgery and did well for 4 additional months. He then returned with the complaint of polyuria, polydipsia, and symptomatic dehydration. Physical examination of the sinus cavity and a CT of the head showed a well-healed cavity without evidence of tumor recurrence or intracranial metastasis. A metabolic and metastatic workup were remarkable for low levels of antidiuretic hormone and elevated liver function tests. A CT of the liver and subsequent liver biopsy confirmed liver metastasis. The etiology of diabetes insipidus (DI) is presumed to be secondary to radiation damage to the pituitary gland; however, surgical trauma, or pituitary metastasis[4] are considerations. The patient opted for palliative treatment of liver metastasis with Cytoxan 1710 mg, doxarubicin 85 mg, and vincristine 2 mg. A moderate tumor response was noted on physical examination. His diabetes insipidus was effectively treated with antidiuretic hormone.

DISCUSSION

Clinically, the most remarkable features of SNUC are the rapid onset of symptoms and the extent of disease at the time of diagnosis. The most common symptoms of SNUC are facial pain and nasal obstruction, followed by proptosis and epistaxis.[2,5] Because early symptoms of SNUC are similar to those found in patients with benign sinus disease, patients often delay seeking and obtaining specialty treatment.

Histologically, SNUC is a small to medium-sized cell malignancy derived from Schneiderian mucosa. The

diagnosis can be difficult based on light microscopic features alone, necessitating IHC characterization for definitive diagnosis. IHC features of SNUC are positive staining for cytokeratin and intermittent staining for epithelial membrane antigen and neuron-specific enolase. There is no staining with S-100 protein or CD-45.[1,5] The differential diagnosis and distinguishing characteristics of SNUC are the subject of several recent articles and are not reviewed here.[1,2,5]

Radiographically, SNUC appears as an expansile lesion with significant bony erosion in advanced cases. Bony erosion is demonstrated on CT and the tumor irregularly enhances with contrast medium. MRI characteristics include isointense with gray matter on T_1 weighted images and irregular enhancement with gadolinium. Intracranial involvement and orbital extension are well-delineated on MRI.

CURRENT TRENDS IN TREATMENT

Approximately 30 cases of histologically proven SNUC have been reported. The first reported cases were from the University of Virginia, and patients presented with advanced lesions which were not considered surgically resectable. These early patients were treated with chemotherapy (specifics of regimen were not reported) and radiation therapy (4 to 60 Gy). Eight of 11 patients were dead of disease at 12 months in this series.[2] Subsequent reports have offered more optimistic survival rates for patients without intracranial spread or distant metastasis who were treated with aggressive multimodal therapy, including surgical resection. A subsequent series from the University of Virginia reported on six additional patients who were treated with a standardized chemotherapeutic regimen of cyclophosphamide, doxorubicin, and vincristine. Patients subsequently received radiation therapy and surgical excision via craniofacial resection. Three of six patients were without disease at 18 to 52 months.[6] Gallo et al[5] reported on 13 patients with SNUC who were treated initially with radiation therapy, 4 to 67 Gy, followed by a chemotherapeutic regimen of mitomycin and 5-fluorouracil. These authors reported a 15% 5-year survival rate for this series of patients. Aggressive, multimodal treatment, including craniofacial resection for patients with advanced SNUC, may offer the best chance of local control, palliation, and survival.

Numerous recent reports of institutional series have examined the efficacy of anterior craniofacial resection for treatment of paranasal sinus and skull base malignancies. As we gain more experience with CF resection for en bloc removal of paranasal sinus malignancies, prognostic factors relating to the tumor are emerging. These patterns, based on the experience of several recent reports, can be summarized as follows.

Tumor grade and histologic type are of paramount importance in predicting patient outcome: patients with high-grade, poorly differentiated tumors have worse chances of long-term survival.[7,8]

Nonesthesioneuroblastoma, poorly differentiated sinonasal tumors with brain, dural[9–11] or orbital involvement[7] have a statistically significant decrease in survival compared with those patients with intracranial or orbital involvement.

Tumor-free surgical margins for craniofacial resection, with orbital exenteration if orbital soft tissue is invaded by tumor are positively related to tumor-free survival status.[12]

Histologic heterogeneity of paranasal sinus/anterior cranial fossa neoplasms makes definitive diagnosis imperative to better predict the behavior of these neoplasms.[13] For example, esthesioneuroblastoma is a treatable entity with a 90% 5-year survival versus 59% for nonesthesioneuroblastoma, based on recent studies at the University of Virginia.[14] Dural invasion by esthesioneuroblastoma occurs early and may not be associated with decreased survival.[7]

The technique of craniofacial resection for paranasal sinus malignancies has evolved over the past 30 years. Today we can offer patients more extensive and safer resections that have very acceptable morbidity, minimal mortality, and relatively little impact on the patient's functional status.[15,16]

We consider the following to be absolute contraindications to surgery: bilateral orbital, optic nerve, or optic chiasm invasion by tumor, frank brain invasion, prevertebral fascia invasion, distant metastasis at initial presentation, or medical condition of the patient precluding surgery. Although it is technically feasible to perform these resections, patient quality of life would not be improved. Limited intracranial and orbital involvement are not contraindications to craniofacial resection.

CONCLUSION

The optimal treatment for SNUC has yet to be determined. It is difficult to ascertain from the small number of patients known to have histologically proven SNUC and the variety of treatments previously used to treat SNUC whether aggressive, combined, multimodal therapy shows significant improvement in survival for patients with orbital or cranial involvement. Our patient, now 16 months after his diagnosis, is alive with distant metastasis and excellent local control. He was able to return to work for a few months after his craniofacial resection before developing liver metastasis and diabetes insipidus. Based on our experience with his malignancy and a review of the recent literature, our future recommendations include:

1. National and international tumor registries for all patients with sinonasal malignancies. These neoplasms are very rare and no single institution has a large series of patients from which to gather significant treatment data. In addition, sinonasal malignancies are an extremely het-

erogeneous histologic group, making any one particular histologic subtype extremely rare. To gain any clinically useful information about the natural history of a particular tumor type, we will need to group our experience as a society.[13]

2. IHC must be done on all sinonasal malignancies that are identified as small to medium cell or "undifferentiated tumors" in order to delineate the cell of origin. IHC is a powerful diagnostic tool that will help to remove the ambiguity in this heterogeneous group of neoplasms.[17]

3. A standardized staging system for ethmoid and sphenoid sinus malignancies based on clinical and radiographic findings must be developed. At present, there is no unified staging system for nonesthesioneuroblastoma tumors outside the maxillary sinus. This contributes to our inability to draw meaningful information from retrospective reviews, compare results with other institutions, or offer our patients good prognostic information. The Kadish staging system[18] utilized for esthesioneuroblastoma is appropriate for SNUC, which occurs in a similar location.

4. Primary care physician education regarding warning signs and the importance of expedient diagnosis for all sinonasal malignancies. Nasal symptoms associated with ocular complaints warrant a full work-up for sinonasal malignancy.

5. A multi-institutional clinical trial and standard protocols to assess the efficacy of aggressive, combined multimodal therapy. The protocol currently used to treat esthesioneuroblastoma at the University of Virginia may be the optimal treatment for SNUC. For Kadish stage C disease, Cantrell[3] recommends chemotherapy prior to radiation and surgery. The protocol is as follows: preoperative and postoperative cyclophosphamide 650 mg/m^2 and vincristine 2 mg/m^2 intravenously on day 1 and 8 of each month for 2 months; another cycle of preoperative chemotherapy is administered if there is CT evidence of tumor response; preoperative radiation therapy, 50 Gy over 5 weeks; and craniofacial resection. The addition of doxorubicin to the chemotherapeutic regimen is recommended for patients with SNUC.[6,14]

As our ability to treat advanced, poorly differentiated sinus neoplasms continues to evolve and improve, we can continue to offer at least some hope to patients with this devastating disease.

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